Fatty Liver

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Medical Biochemistry& Molecular Biology

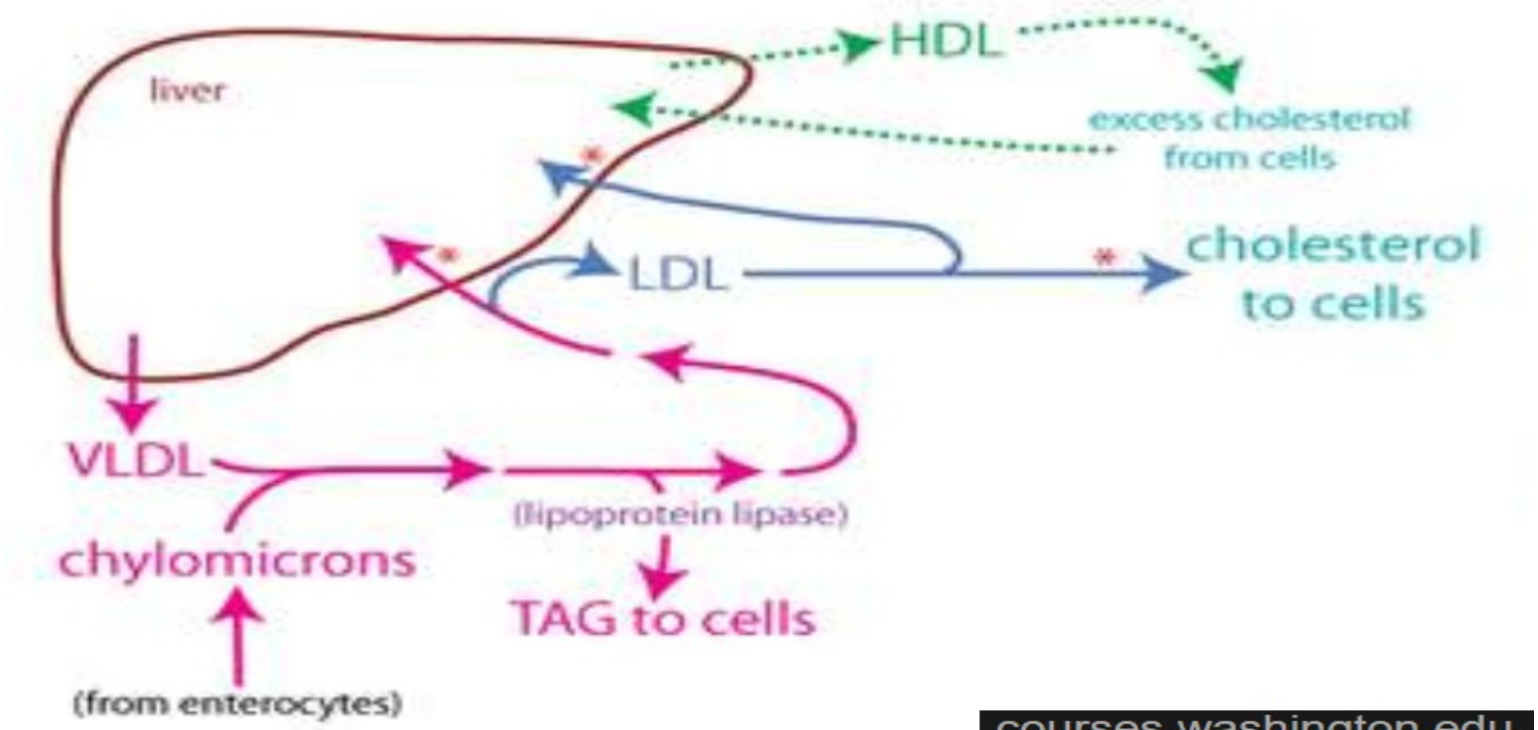
INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1. Define the fatty liver
2. Explain the factors regulating fat content of the liver.
3. Discuss types of fatty liver and causes of each type.
4. Analyze the biochemical changes associated with fatty liver.
5. Identify the lipotropic factors that facilitate mobilization of fat from the liver.

Role of liver in lipid metabolism

- Liver plays a central role in the metabolism of various types of triglycerides, steroids, phospholipids, plasma lipoproteins and fat soluble vitamins



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:A) Role in TAG and FA metabolis

- ***Uptake*:** After meals, liver takes up about 30% of the FFA and most glycerol of absorbed fats.
- ***Synthesis:*** Liver converts part of the absorbed sugar into TAG. Also, FA that produced from hydrolysis or after feeding of fats is converted into TAG.
- ***Mobilization:*** TAG are mobilized from the liver into the blood in the form of VLDL.
- ***Oxidation:*** FFA are oxidized by the liver to supply energy.
- ***Ketogenesis*:** During starvation, ketone bodies are synthesized in the liver and released into blood to extrahepatic tissues to serve as alternative source of energy.

B) Role in phospholipids metabolism:

Phospholipids are synthesized and provided to the plasma by the liver.

C) Role in steroid metabolism:

Liver is the major site for cholesterol synthesis. It also removes cholesterol from the blood to use it in the synthesis of vitamin D3 and bile.

D) Role in metabolism of plasma lipoproteins:

It has major role in the metabolism of different types of lipoproteins

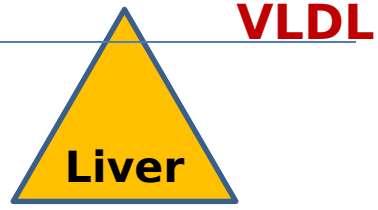
Synthesis of hepatic TAG → immediate stimulus for the formation and secretion of **VLDL**.

The fatty acids used are derived from two possible sources:

(1) Synthesis within the liver from acetyl-CoA derived mainly from carbohydrate (Well-fed condition).

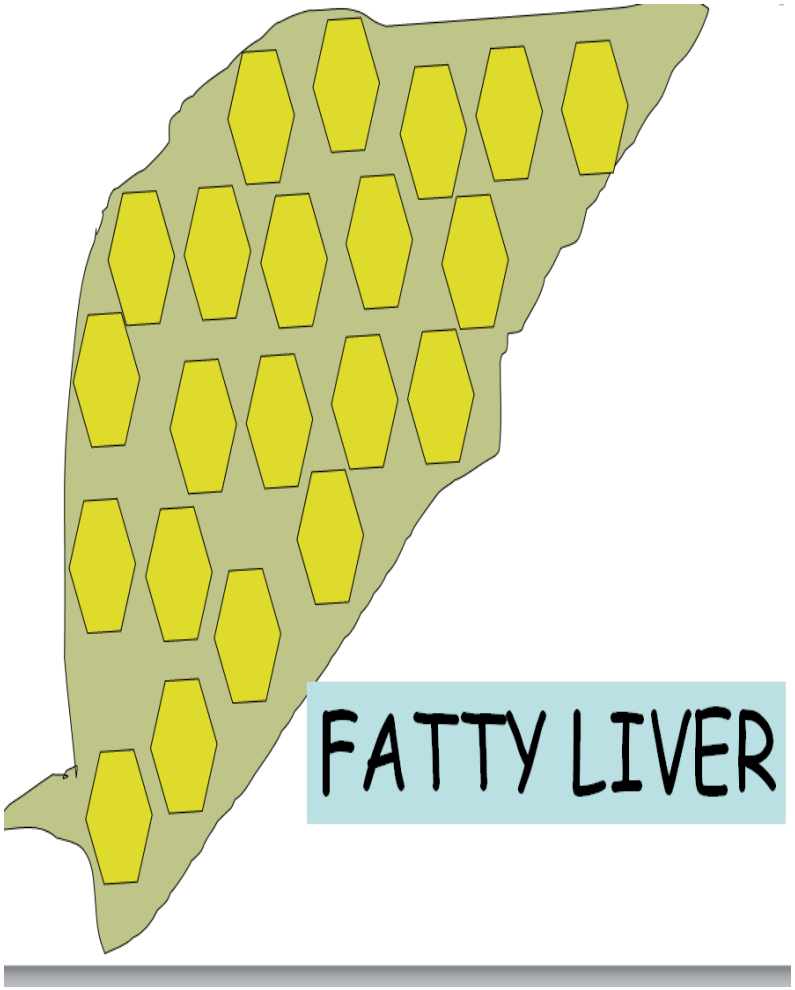
(2) Uptake of FFA from the circulation (in case of

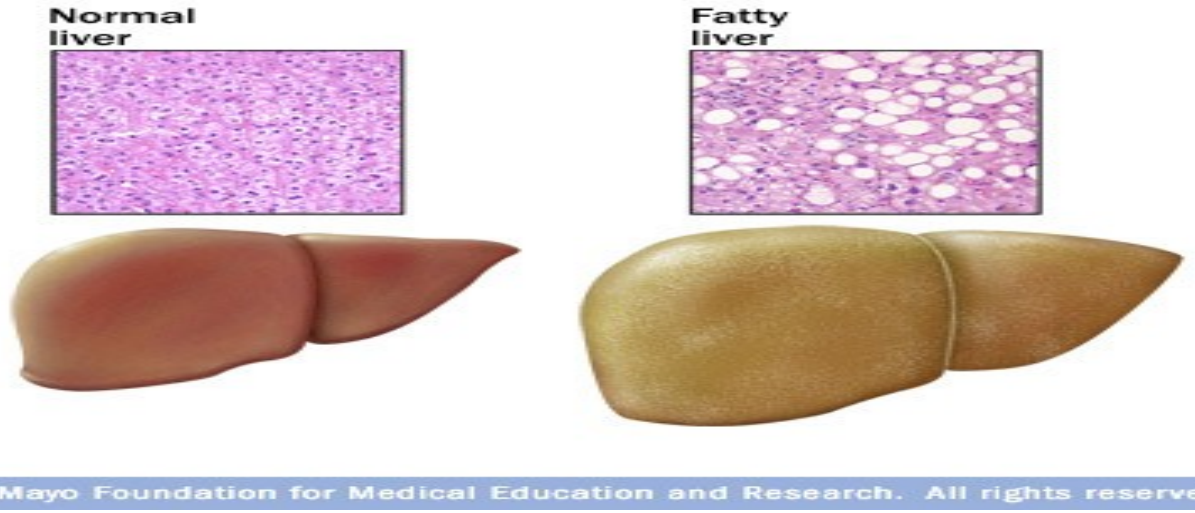
As TAG does not normally accumulate in the liver under this condition, it must be inferred that it is transported from the liver in VLDL as rapidly as it is synthesized



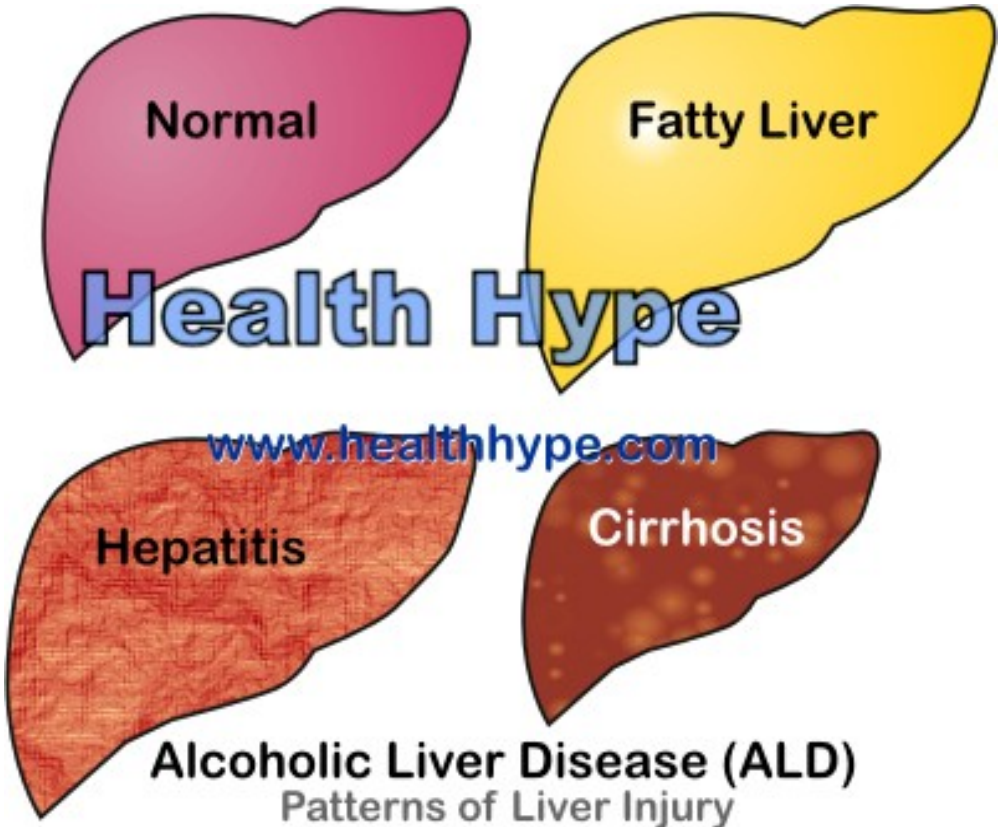
Fatty liver

- it is a reversible condition as large vacuoles of triglyceride fat accumulate in liver cells via the process of steatosis.
- The accumulated TAG results in liver enlargement , fibrosis and cirrhosis . The normal lipid content in the liver about **4% of its weight** (about75% PL+25% TAG)

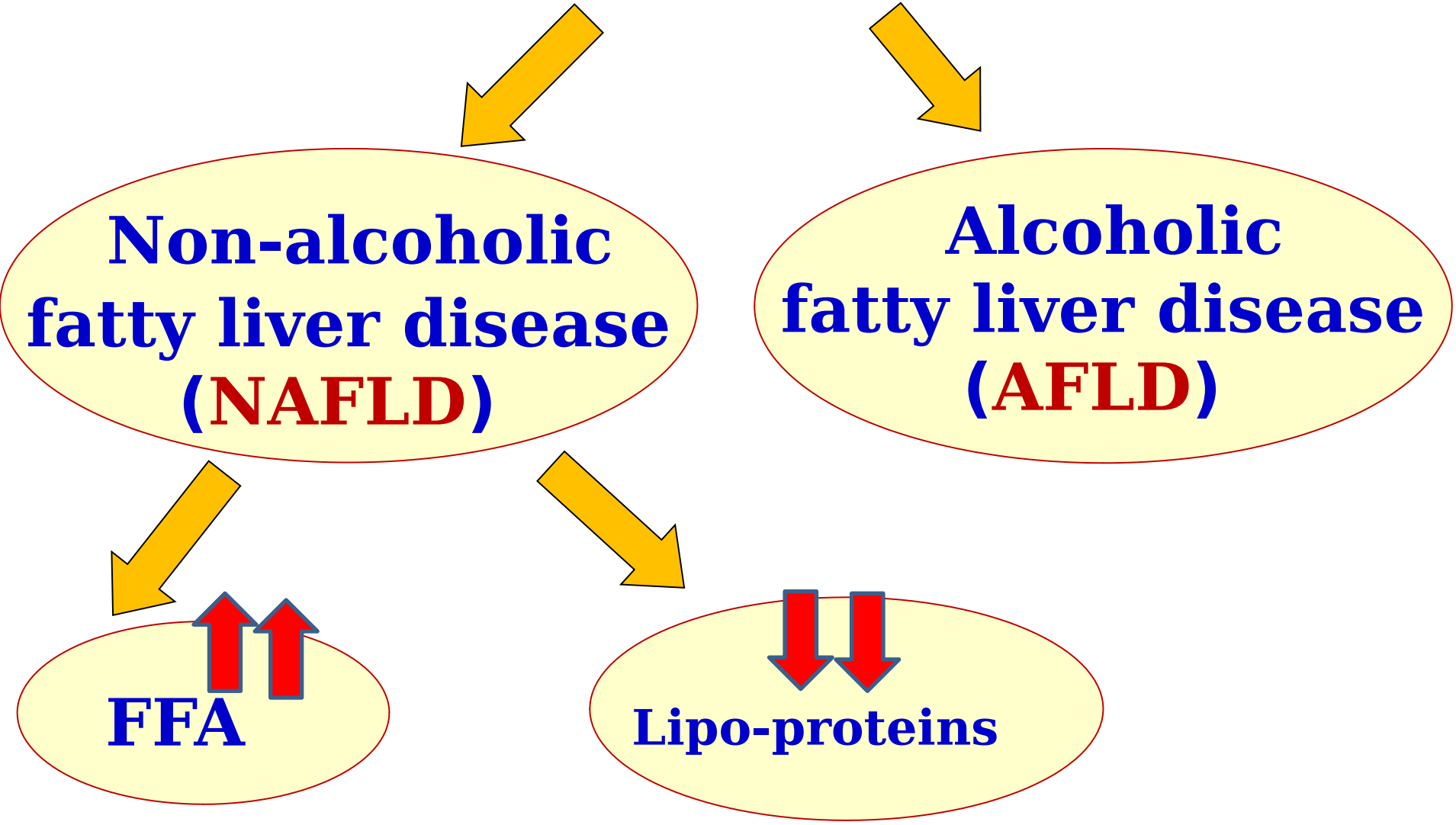




- When accumulation of lipids in the liver becomes chronic, fibrotic changes occur in the cells that progress to **cirrhosis and impaired liver function.**



Types Of Fatty Liver



Causes of Non-Alcoholic fatty :liver disease (NAFLD)

1. Metabolic
2. Nutritional
3. Drugs and toxins

Non-Alcoholic fatty liver disease (NAFLD)

A. Metabolic

1. Abetalipoproteinemia,: Decreased mobilization of TAG from liver to extrahepatic organs via VLDL, leads to accumulation of fats in liver. This is known as metabolic block in the production of plasma lipoproteins

NB: VLDL contains Apo B-100 (coded by Apo B .gene in liver)

2. Glycogen storage diseases, inability to store glucose as glycogen, converting it to TAG, if this exceeds the capacity of the liver to produce VLDL **fatty liver**

3. **Metabolic syndrome (uncontrolled DM with**

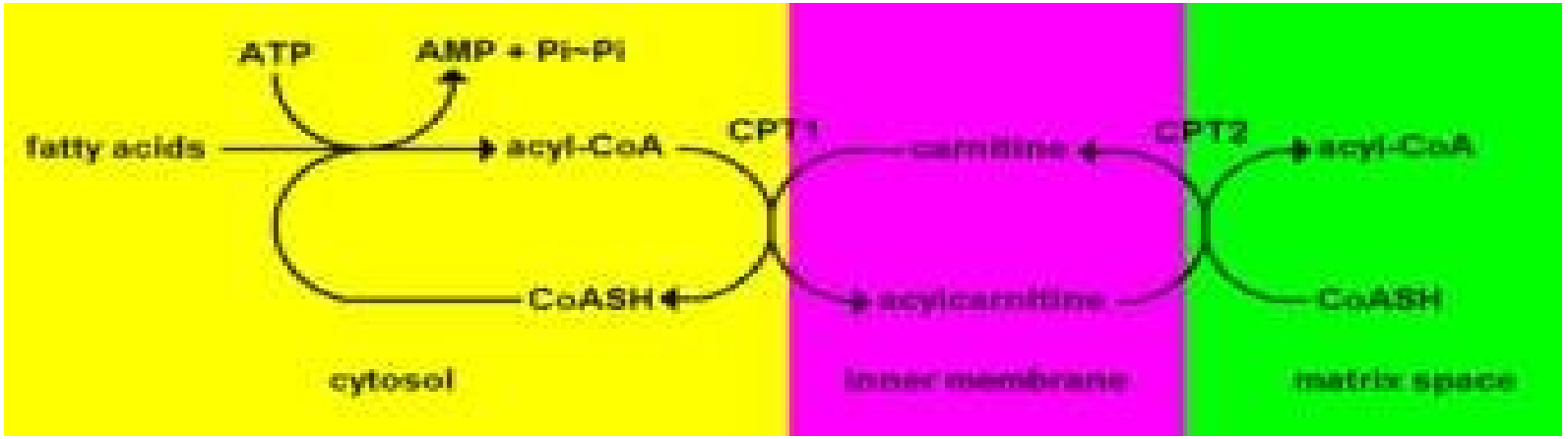
B. Nutritional: (Deficiency and unbalanced diet)

1. Fat-rich diet ⟹ uptake of fats by liver, if this exceeds the capacity of the liver ⟹ to produce VLDL ⟹ **fatty liver**

2. Carbohydrate-rich diet: overload the capacity of liver to store it as glycogen ⟹ converting it to TAG, if this exceeds the capacity of the liver ⟹ to produce VLDL ⟹ **fatty liver**

B. Nutritional; con.

3.Esterification of FA due to **carnitine deficiency** lead to **fatty liver**.



4.Starvation: Increased mobilization of FA from adipose tissue to liver cells

5.Deficiency of lipotropic factors: Decreased mobilization of TAG from liver to extrahepatic organs via VLDL leads to accumulation of fats in liver.

C. Drugs and toxins

- e.g. methotrexate, glucocorticoids, tamoxifen, Carbon tetrachloride and puromomycin. Also, environmental hepatotoxins (e.g. phosphorus, toxic mushroom) .
- They inhibit protein synthesis including apoB100.

D. Other :Inflammatory bowel disease, HIV

Summary

The following mechanisms could be responsible for the occurrence of fatty liver:

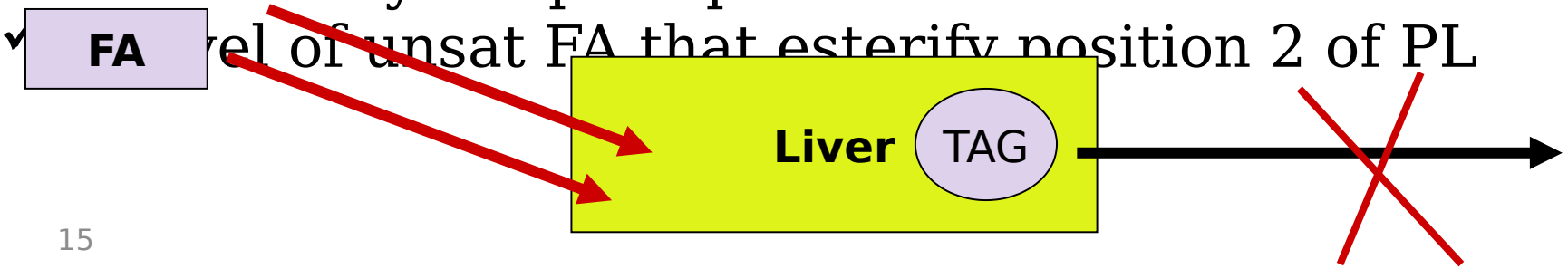
1.↑ mobilization of FA (from diet or from adipose tissue as in starvation or DM) → elevated plasma FFA and their hepatic uptake →activated to acyl CoA =increased TAG synthesis.

2. **Failure of liver to synthesize VLDL**, could be due to:

- failure to synthesize apoB100
- failure to release VLDL.
- failure to synthesize phospholipids due to :

✓ deficiency of lipotropic factors

✓ level of unsat FA that esterify position 2 of PL



Alcoholic fatty liver disease -2 :(AFLD)

The fat accumulation in the liver is caused by a combination of:

Impaired fatty acid oxidation

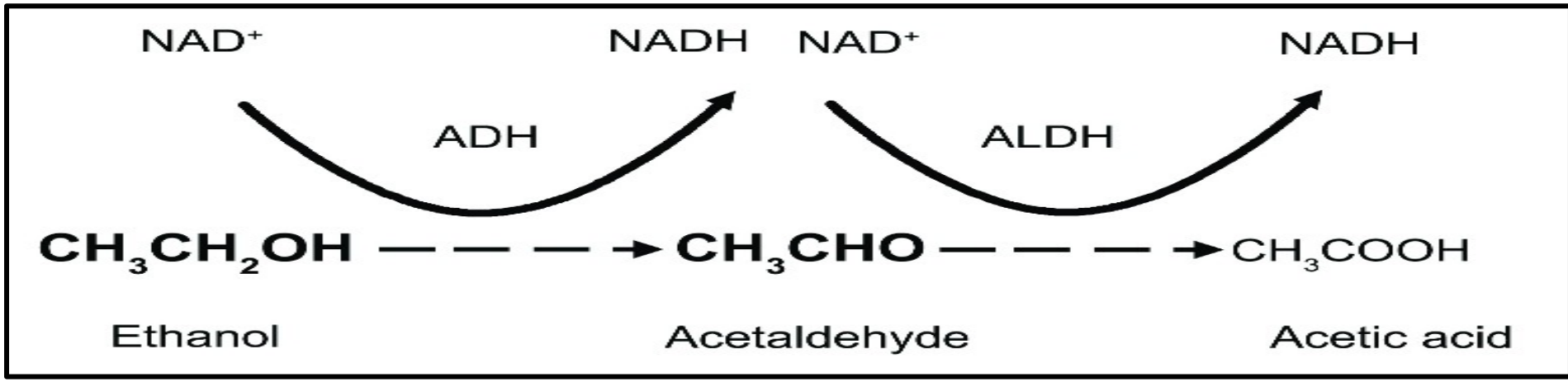
+

Increased lipogenesis

:Alcoholic fatty liver disease (AFLD) -2

Oxidation of ethanol by alcohol dehydrogenase leads to excess production of NADH

??HOW

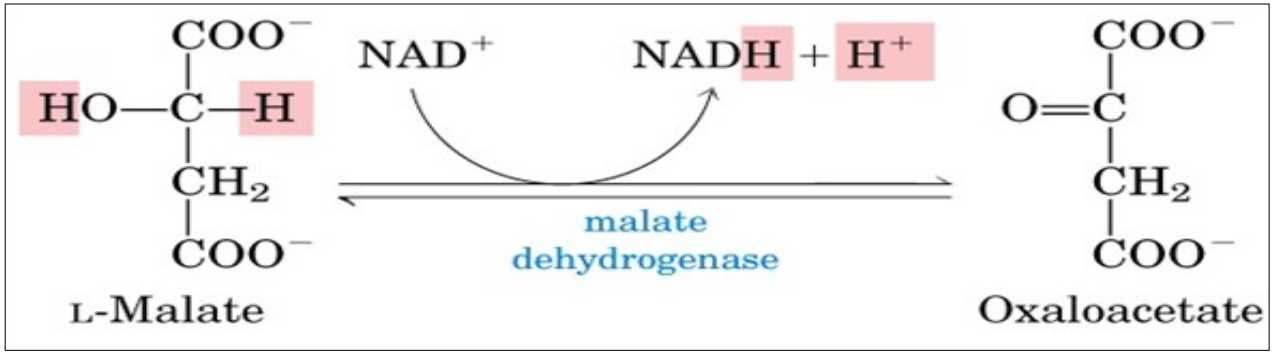


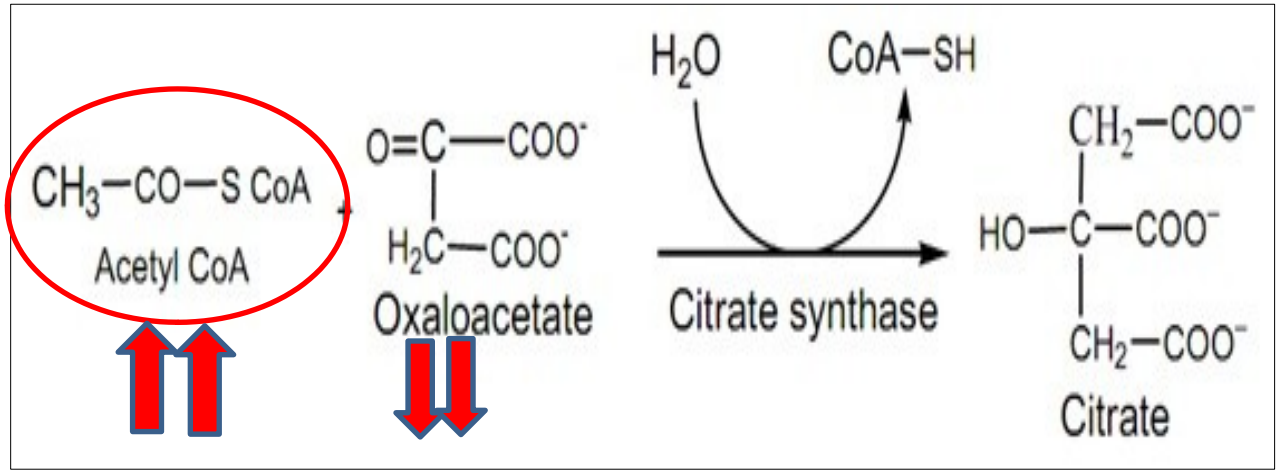
Excess production Of NADH by

1. Excess NADH with more energy production ……. Result in inhibition of FA oxidation

2. *Excess NADH* Shift oxaloacetate to malate

TCA cycle





3. Excess NADH: resulting in increase TA synthesis

Accumulated acetyl coA

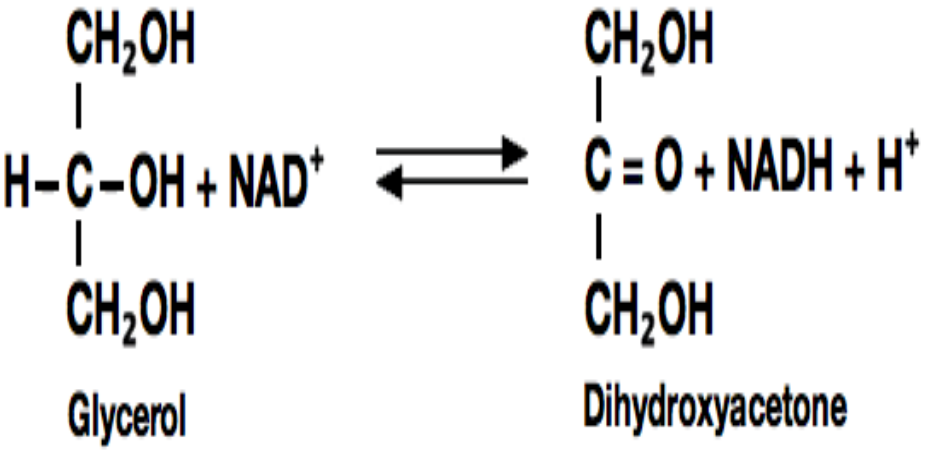
Excess NADH+H

ketogenesis

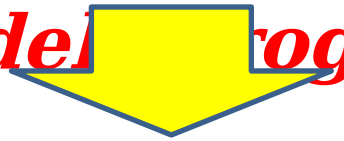
FA synthesis

Glycerol 3-P

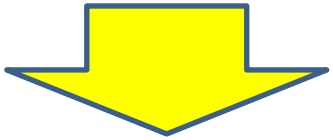
TAG



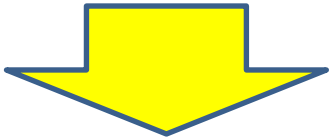
Oxidation of Ethanol by *alcohol dehydrogenase*



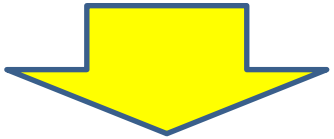
Excess production Of *NADH*



***Interferes with* other pathways (*FA oxidation* and *TCA cycle*)**

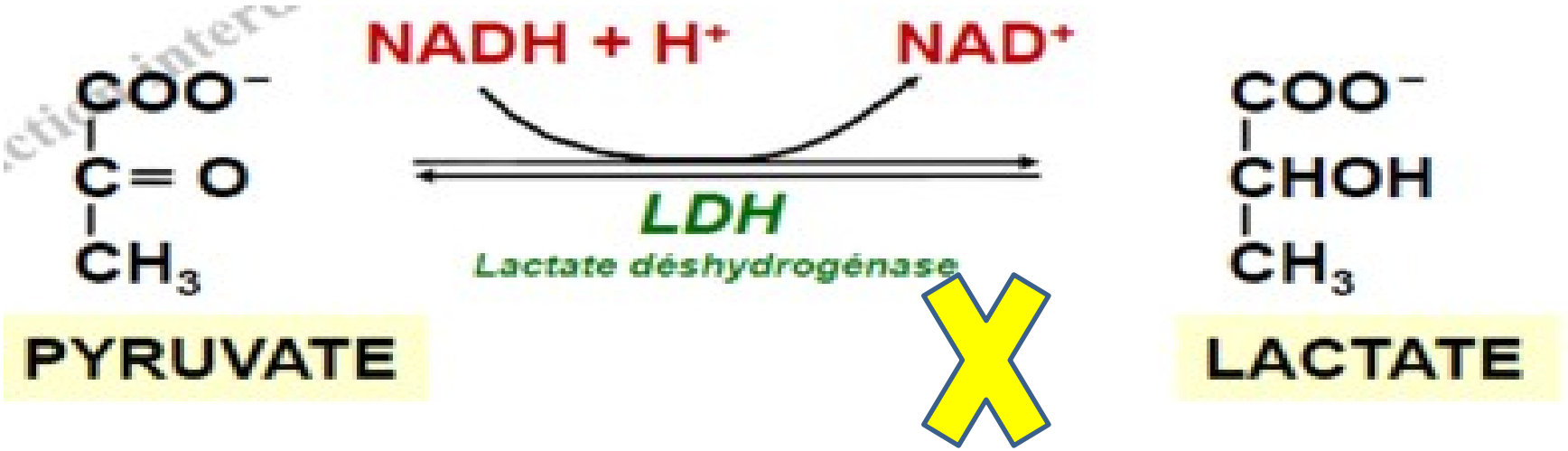


***Fatty acids* accumulate**



***TAG* deposition in liver**

Increased (NADH)/(NAD+) ratio also causes .4
,increased (lactate)/(pyruvate)
resulting in lactic acidosis, which
decreases excretion of uric acid, aggravating gout



Summary

Alcoholic fatty liver

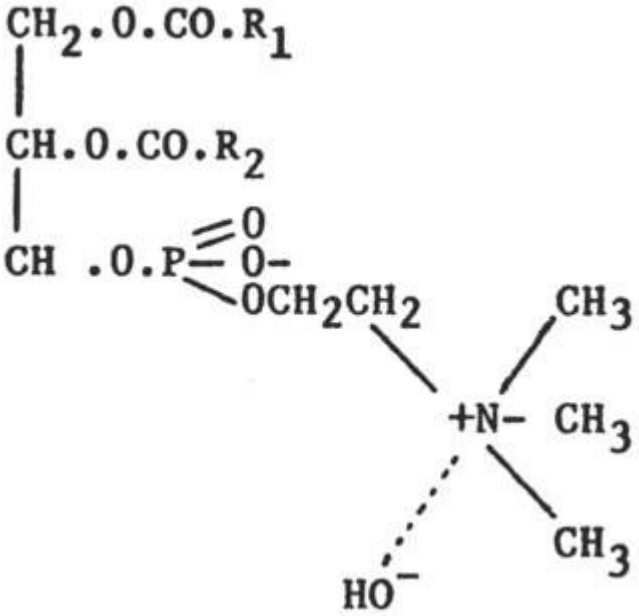
- Alterations in **fatty acid metabolism** occur as fatty **acid oxidation is inhibited by the high levels of NADH**.
- **Fatty acids accumulate in the liver, produce triacylglycerols**, and increase the production of VLDL. The **export of VLDL is diminished in chronic alcoholics, leading to a fatty liver**, **due to imbalance of fat accumulation &an impairment in protein synthesis due to chronic liver dysfunction**

Lipotropic Factors

- These are substances that protect against and cure fatty liver.
- They include mainly the substances **essential for synthesis of phospholipids** which are easily to mobilize from liver and less liable to deposit in liver cells

Lipotropic substances are:

1. **Choline, inositol, serine and ethanolamine** (constituents of PL)
2. **Methionine and betaine** (methyl donors for choline)
3. **Casein** (rich in methionine).



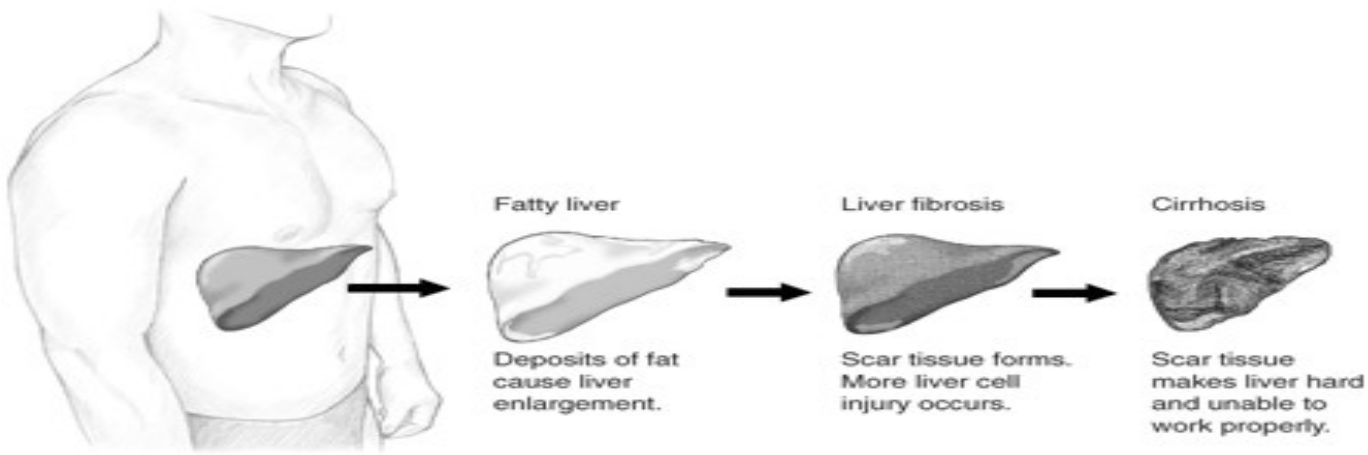
phosphatidyl choline

Lipotropic substances ; con.

4. **Estrogen** inhibits HMG-CoA reductase (the key enzyme of FA synthesis).
5. **Essential FA**, eg, linoleic acid (Unsat.FA enter in PL synthesis)
6. **Vits. B12 , folic acid, pantothenic acid** (help transmethylation reactions for choline PL synthesis)
7. **Vit. E & selenium** : protect against FFA oxidation
8. **pyridoxine (B6)**: essential cofactors for enzymes involved in various metabolic activities, which include amino acid, fat, and glucose metabolism e improve liver

How to protect your liver?

- Avoid High-fat and high-glycemic-index foods.
- No alcoholic beverages.
- Watch your drugs.
- Be careful with aerosol sprays.
- Healthy diet, vitamins and antioxidants are required for healthy liver



Test your self

- A 67-year-old male with extreme obesity and type II diabetes mellitus controlled by diet alone has persistent ALT and AST elevation 3 times the normal limit with normal ALP. He a diagnosed a fatty liver; which of the following not cause fatty liver

a. Chronic alcoholism
b. Excessive intake of sweet
c. Excessive intake of butter
d. Intoxication with carbontetrachloride
e. Excessive intake of carnitine

SUGGESTED TEXTBOOKS

- "Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R.Ferrier
- "Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W.Rodwell.
- Fundamentals of Clinical Chemistry (Tietz) Sixth
- "Textbook of Biochemistry with Clinical Correlations" by T.M.Devlin
- www.namrata.co- ***Biochemistry for medics***